CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ACIFLUORFEN, SODIUM SALT

Chemical Code # 002218, Tolerance # 00383
SB 950 # 246, EPA Reg. # 7969-0-

April 21, 1994

I. DATA GAP STATUS

Combined, rat:	Data gap, inadequate study, no adverse effect indicated
Chronic, dog:	Data gap, inadequate study, no adverse effect indicated
Oncogenicity, mouse:	Data gap, inadequate study, possible adverse effect indicated
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rabbit:	Data gap, inadequate study, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	Data gap, inadequate study, possible adverse effect indicated

DNA damage: No data gap, possible adverse effect

Neurotoxicity: Not required at this time.

Toxicology one-liners are attached.

The Summary considers all SB-950 mandated studies on file as of the 4/21/94 DPR data index printout. This included evaluations of studies through Document No. 383-067, Record No. 128901.

In the "one-liners" below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T940421

Original: Kishiyama, Aldous, and Gee, 4/21/94.

NOTE: The majority of studies reviewed to date are not acceptable, and corrections of deficiencies will require responding to concerns stated in the DPR reviews. Aldous, 4/21/94.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

383-049 115106 [the pathology report is found in Document 383-050, Record No. 115107]. Barnett, J.W. (Principal Investigator), "Evaluation of the potential oncogenic and toxicological effect of long-term dietary administration of "Tackle" to Fischer 344 rats". In-life portion was performed at Gulf South Research Institute (Atchafalaya Basin Lab in New Iberia, LA): pathology by WIL Research Laboratories, Inc., Cincinnati, OH. Report dated 3/30/83. GSRI Project No. 413-985-41. Acifluorfen, apparent purity about 78%, was admixed with the feed at nominal concentrations of 0, 25, 150, 600, 2500 or 5000 ppm to 73 Fischer 344 rats/sex/group for 104 weeks. Of these, 8/sex/group were sacrificed after 1 year. The 5000 ppm group began the study at 10 ppm, however this group was treated with 5000 ppm after the fourth week and until the end of the study. NOEL = 25 ppm (corneal opacities: only in males, and only detected at terminal sacrifice). NOEL excluding corneal opacities = 600 ppm. Common findings at 2500 ppm included reduced body weight (both sexes), reduced globulin levels (both sexes), increased liver weight, nephritis and/or pyelonephritis, in some cases with papillary necrosis (females), acidophilic liver cells (females). The latter findings, along with high incidence of stomach ulcers and minor anemia, were found in both sexes at 5000 ppm. The high dose led to high mortality during the second year of the study, and greatly exceeded "MTD" criteria in both sexes based on body weight decrements. **Not acceptable**, upgradeable (major problems are lack of GLP signoff in a study having many discrepancies, and insufficient characterization of test article). **No adverse effect** indicated. (Kishiyama and Aldous, 4/13/94).

383-051 115108 Evaluation by Hauswirth, J.W. et al. of Record Nos. 115106 & 115107, focusing on the extent to which the study meets FIFRA guideline criteria. The major concerns

of the DPR review (see above) are not addressed in this evaluation. Aldous, 2/7/94 (no DPR worksheet of this evaluation).

048 91833. Duplicate of 115106 & 115107.

383-008 002184 Coleman, M.E. (Study Director) "Three and Twenty-Four Month Oral Safety Evaluation Study of RH-6201 in Rats (DRC 5800) A Feeding Study in Rats", (Dawson Research Corp., DRC 5800, 10/26/78). RH-6201, 39.8 & 39.4% a.i., administered admixed with the feed at concentrations (changed over time) of 0, 25 (increased to 354 and to 1680), 15 (increased to 21 and to 30) 80 (increased to 127 and to 1080) and 1080 ppm and fed to 75 Charles River rats/sex/group. Initially classified as indicating adverse effects due to changes in the liver (centrilobular hypertrophy) and testes (decreased weight) [note status update, below]. UNACCEPTABLE (study is complete but a major dosing problem). (J. Remsen, 7/9/85). **NOTE**: This study was re-examined in 1994 with respect to "possible adverse effect" designation. That designation is no longer appropriate because (1) the findings are not of substantial toxicological concern, and (2) a study subsequently submitted (Gulf South study with DPR Record No. 115106) covers a much wider dosage range, and does not indicate a "possible adverse effect". Thus there is no adverse effect indicated for the rat chronic/oncogenicity study type. Aldous, 4/13/94.

009 2186 Individual body weight data for 2184.
010 2187 Individual food consumption data for 2184.
011 2188 Addendum to 2184.
030 2254 Amendments to 2184.
031 2255 Amendments to 2184.
032 2256 Amendments to 2184.
033 2257 Amendments to 2184.
034 2258 Amendments to 2184.
038 26466 Analysis of feed (studies 2184, rat; 2193, dog; & 19871, mice).
005 26462 Duplicate of 26466
034 26464 Correction of study 2188 for study 2184.
012 26463 Feed analysis data (this appears to be the information given Record No. 002195 in the data index.)
001 2121 Three-month interim report for 2184.
001 2103 Six-month interim report for 2184.

CHRONIC TOXICITY, RAT

See combined, rat

CHRONIC TOXICITY, DOG

383-052 115109 Griggs, L.M.P., "Two year dietary toxicity study in dogs", IRDC Study No. 450-039, 6/30/83. Acifluorfen (Tackle*) (cream to beige-colored powder, purity apparently 22-24%, was administered in diets of beagles at 0, 20, 300, or 4500 ppm. Six dogs/sex/group were allocated for the 2-yr study, and an additional 2/sex/group were sacrificed at 6 months. **No adverse effects indicated.** NOEL = 300 ppm. This was based on thin appearance and associated reduced body weights, hematology changes suggesting mild anemia, increased weights of liver and kidneys, and liver pathology such as fatty vacuolation, congestion, minor lymphocytic infiltration. In addition, there was brown pigmentation of liver, gall bladder, and kidneys: pigments were often associated with macrophages and appeared to be bile pigments.) **Not**

acceptable, **upgradeable**. Clarifications required include (1) purity of test article and (2) whether the dose levels indicated in the report represent the technical material, or whether levels were adjusted for purity to provide "ppm" levels of pure active ingredient. Also, the report should provide stability data of the test article prepared in the "base solution" and of the treated diet. Study is otherwise acceptable. (Kishiyama and Aldous, 1/20/94).

383-053 115111 Evaluation of Record No. 115109, above, with respect to deviations from U.S. EPA guidelines. The evaluation includes statements that the submitter has access to the raw data upon which the report was based, and certification that the report accurately represents those data. This evaluation characterizes the test article as technical grade, purity 22-24%. No DPR worksheet. Kishiyama and Aldous, 1/24/94.

383-012 002193 Piccirillo, V.J., "104-Week Toxicity Study in Dogs" (Hazleton Laboratories America Inc., Project No. 417-357, 9/11/78). RH-6201, 40% a.i., was admixed with the feed at concentrations of 0, 50, 300, 1800 (1800 ppm [wk. 1-17], 3600 ppm [wk. 18-27] and 5400 ppm [wk. 28-104]) ppm and fed to 4-6 Beagle dogs/sex/group for 104 weeks. UNACCEPTABLE. Dogs too old at start of experiment and also dosage was increased during the course of the study until toxicity was achieved (increased liver and kidney weights; hematological alterations) at the final increase (5400 ppm) for the high dose group, (J. Remsen, 7/8/85). **NOTE**: This study was originally classified by CDFA as indicating a "possible adverse effect". That designation is no longer appropriate because (1) the findings are not of substantial toxicological concern, and were limited to a relatively high dose, and (2) a study subsequently submitted (IRDC study with DPR Record No. 115109) covers a similar dosage range, appears to be upgradeable, and does not indicate a "possible adverse effect". Thus there is no adverse effect indicated for the dog chronic study type. Aldous, 4/13/94.

001 26451 Appendix to 2193. Progress report.

383-053 115110 Evaluation of acceptability of data in Record No. 002193, above. The evaluation found this study less readily "upgradeable" than Record No. 115109. No worksheet of the evaluation by DPR. Aldous, 1/24/94.

012 2192 Analysis of dog feed for study 2193.

ONCOGENICITY, RAT
(See combined, rat)

CHRONIC/ONCOGENICITY, MOUSE

383-054 and -055 115112 and 115113 Barnett, J.W. (Principal Investigator), "Evaluation of the potential oncogenic and toxicological effect of long-term dietary administration of Tackle to B6C3F1 mice", Gulf South Research Institute, New Iberia, LA, November 3, 1982. GSRI Project No. 413-984-41. B6C3F1 mice were treated in the diet for up to 18 months with 0, 625, 1250, or 2500 ppm Acifluorfen (the same lots were used as in the concurrent rat combined study, and the same clarifications will be required for both studies about the identity of the test article). Sixty/sex/group were initiated at each dose level, with 10/sex/group allocated for 1-yr interim sacrifices. No systemic NOEL was achieved. Dose-related reductions in body weights were noted for both sexes at all dose levels. Also, females had no apparent NOEL for papillomas of the nonglandular mucosa of the stomach, based on a positive trend test (in males, these papillomas were limited to high dose mice). High dose males and females had marked increases in hepatocellular adenomas and carcinomas. In addition, low-dose males had lesser, but statistically significantly elevated incidence of hepatocellular adenomas, and a non-significant elevation was evident for mid-dose males. Study is **not acceptable**, possibly upgradeable (see part VI.A. of DPR review). Tumors of the liver and of the stomach are **"possible adverse effects"**. Kishiyama and Aldous, 4/7/94.

047 91832. Same study as 054 115112 and 055 115113. However, contains the deviation report of a dosing error (p. 116 in Appendix C) that was referenced but not included in 054 115112.

383-056 Evaluation of merits and weaknesses of Record No. 115112, above, by J. Hauswirth on behalf of BASF: she considered the study to be acceptable. Also, this document contains a 9/30/87 memorandum by U.S. EPA, which considered the collective mouse studies (Record Nos.

115112 and 019871) to be adequate for the mouse oncogenicity data requirement (see last page, this document). The U.S. EPA document concluded that Acifluorfen was a category B2 oncogen, based on mouse stomach and liver tumors, and considering structural relationship of Acifluorfen to several compounds which elicit mouse liver tumors. Aldous, 2/9/94, no worksheet (since this record is not a "study").

056 115114 also contains a section on the significance of changes from the acceptance criteria for 054 115112 and 055 115113.

383-038 019871 Goldenthal, E.I., "Lifetime dietary feeding study in mice with RH-6201 (Blazer) - 'In life' Report", IRDC Study No. 285-013a, March 6, 1979. The pathology report was presented in 383-039:019872 [Barthel, C.H., Feb. 9, 1979]. A summary of the acceptability criteria and of the results of the above study had been prepared by J.W. Hauswirth (383-056:115115). The initial survey of toxicology data done by CDFA [J (Remsen) Gee, 7/11/85] had identified the study as unacceptable due to study design deficiencies, with no adverse effect indicated. That assessment was made on the basis of the 12-month report (Record No. 019871), whereas the majority of tumors were not evident until later in the study. The pathology report (Record No. 019872) was evidently not identified as a part of this study in the CDFA survey of toxicology studies done in 1985. The DPR review of 1994 considered all three records cited. RH - 6201, 39.4-40.5% active ingredient, was fed in diets at concentrations of 7.5, 45.0 and 270 ppm to 80 CD-1 mice/sex/group. There were two essentially equivalent control groups "shared" between this study and a concurrent study. The 270 ppm group had been started at 1.25 ppm, but dose level was raised to 270 ppm at week 17 due to lack of apparent toxicity at 45 ppm. Interim sacrifices of ten mice per sex per group were made at 3 & 12 months. High dose females had increased incidence of hepatocellular adenomas (a "**possible adverse effect**"). There were no substantive associated pre-neoplastic lesions, making this study a poor candidate for quantitative risk assessment. Study remains "unacceptable". Aldous, 4/21/94.

383-039 19872 Barthel, C.H., [Pathology report for Record No. 019871, above]. Histopathology for mice which died following week 52 of the study was done by Barthel, a consulting pathologist. He noted the following statistically significant increases in liver lesions: focal cellular alteration in 270 ppm males; and focal pigmentation in 7.5 ppm and 270 ppm females (but no effect at 45 ppm). All male treated groups had higher incidence of hepatocellular carcinoma than controls, however there was no dose-response, and no statistical significance (2-way comparison of either control group vs high dose group, one-tailed Fisher's Exact Test). Aldous, (considered in review for Record No. 19871, above).

383-037 019868 Analysis of tumor incidence in Record No. 19871, above, by J.M. Smith. Statistical comparison of high dose female tumor yields vs. one of the two equivalent control groups yielded a non-significant result by Chi Square analysis. The DPR evaluation of 4/21/94

utilized the combined female controls for statistical comparisons because both control groups are considered equivalent, and found a statistically significant increase in hepatocellular tumors in high dose females (see review for Record No. 19871, above). No separate worksheet for this record. Aldous, 4/21/94.

056 115115 Summary of 19871, including discussion on acceptability status (data cited in 1994 re-evaluation of Record No. 019871, above).

037 019869 and 019870 Appendix (EPA re-evaluation) to 19871.

001 026449 Three month interim report for 19871.

012 002194 Supplement pathology report to 026449.

001 026450 One month interim report for 19871.

038 026465 Feed analysis for study 19871.

REPRODUCTION, RAT

383-057 115117 Lochry, E.A., Study Director, "Reproductive effects of Tackle* administered orally in the feed to Crl:COBS*CD*(SD)BR rats for two generations", Argus Research Laboratories, Inc., Perkasie, PA. (Subcontracts: Bio/dynamics, Inc. (diet preparation and analysis) and HistoResearch Lab. Inc. (slide preparation and histopathology). January 20, 1986. This was a 2-generation study: 1 mating trial per generation, 35 rats/sex/group in F0 generation, 40/sex/group in F1. Dose groups were 0, 25, 500, and 2500 ppm of the sodium salt of Acifluorfen (technical material was a solution containing about 21% sodium Acifluorfen, but dietary concentrations were based on analytical standards of the free acid). Maternal toxicity NOEL = 25 ppm (kidney tubular dilatation, outer medulla, females only). Mating and fertility effects NOEL = 2500 ppm (highest dose tested). Developmental effects NOEL = 500 ppm (retarded pup growth). Common findings in F0 and F1 rats at 2500 ppm included statistically significantly lower body weights, decrements in food consumption (particularly in females during lactation), frequent gross kidney lesions such as dilatation of pelvis in F1 males, white colored and/or raised areas (typically diagnosed microscopically as pyelonephritis) in F1 females, and tubular epithelial necrosis (high dose F0 and F1 females). Some deaths at 2500 ppm were attributed to treatment, particularly in F1 females, and associated with kidney damage. Study is **acceptable, and there were **no adverse effects**. Kishiyama and Aldous, 3/15/94.

383-058 115118 Neal, B.H., 5/24/90 evaluation of acceptability criteria for study 383-057 115117, above. The study was found acceptable on its first DPR review, and this evaluation (which also found the study acceptable) does not require a DPR worksheet. Aldous, 2/24/94.

012 2190 Goldenthal, E.I., "Three Generation Reproduction Study in Rats RH-6201 LC", (IRDC, 7/28/78). RH - 6201, 40.5 -39.4% a.i. admixed with feed at concentrations of 0 (acetone/water), 5, 30 or 180 ppm and fed to 10 male and 20 female CD rats (P1)/group and for the P2 and P3 generations, the low dose (5 ppm) increased to 540 ppm due to lack of toxicity in low P1 group. No adverse effects indicated, UNACCEPTABLE, not upgradeable (dose change during study progress). (J. (Remsen) Gee, 7/10/85).

TERATOLOGY, RAT

383-059 115119 Florek, M.C., "Teratogenicity study of TACU 06238001 in pregnant rats", Argus Research Laboratories, Inc., Perkasie, PA, 4/24/81. Study No. 113-004. Acifluorfen (sodium salt), designated in this report as "TACU 06238001", purity 81.2%, was administered by gavage at concentrations of 0 (10 ml/kg deionized water as vehicle), 20, 90 or 180 mg/kg/day to 25 mated female Crl:COBSTCDT(SD)BR rats per group during days 6 thru 19 of gestation. Maternal NOEL = 20 mg/kg/day (excessive salivation). Developmental NOEL = 20 mg/kg/day (delayed fetal development, indicated by delayed ossification and increased incidence of a slight degree of dilatation of lateral ventricles). Common findings at 180 mg/kg/day included deaths of two 180 mg/kg/day dams; reduced dam body weight gain; and several characteristic clinical signs, including excessive salivation, chromorhinorrhea, and urine-stained abdominal fur. **No adverse effects**. **Not acceptable, upgradeable** (needs clarifications about the nature of the test article and methods for dosing solution preparation). Kishiyama and Aldous, 4/13/94.

383-060 115120. Sponsor’s analysis of 115119. Includes study acceptance criteria. No worksheet is needed. Aldous, 3/1/94.

TERATOLOGY, RABBIT

383-061 115121 Lightkep, G.E. (Study Director), "Teratogenic potential of TACU 06238001 administered orally via stomach tube to New Zealand White rabbits" [Project 113-003P]. Argus Research Laboratories, Inc. [no final draft has been submitted: in-life phase was apparently 9/14/80 to 10/17/80]. Acifluorfen (free acid) was neutralized to form the sodium salt, and administered by gavage to 16 NZW rabbits per group at 0, 3, 12, or 36 mg/kg/day from days 6-29 p.c. The 3-part submission received by DPR does not contain the text of the final report with summary tables, although extensive raw data pages are present. Individual data, to the extent legible, do not indicate untoward effects. The final report, containing summary tables, and at least "Methods", "Results", and "Discussion" sections, is requested. Aldous, 4/13/94.

061 115121 (part 1). Protocol for 115121 (part 2) and raw data for dose range-finding study for 115121 (part 2).

061 115122 (part 3). Dose range-finding study for 115121 (part 2).

062 115123. Sponsor's summary of 115121 (part 2). Also, summary of dose range-finding study for 115121 (part 2). This summary does not make the submission "complete" enough for formal DPR review. Aldous, 3/2/94.

383-012 002191 Piccirillo, V.J., "Teratology Study in Rabbits RH-6201 LC" (Final Report), (Hazleton Laboratories America Inc., Project no. 417-374, 9/2/77). RH - 6201, LC, 39.8% a.i., administered by gavage at concentrations of 0 (distilled water), 20, 60, or 180 mg/kg/day to 15 artificially inseminated New Zealand White rabbits/dose group. Skeletal analysis data missing, liquid concentrate formulation of test article used, rationale for dose selection not given, excessive mortality. UNACCEPTABLE. (J. Remsen, 7/10/85). NOTE: This study was considered in the 1985 CDFA review to indicate a "possible adverse effect", due to excessive mortality of does at the high dose. The "possible adverse effect" designation is no longer appropriate because (1) although the higher two dose levels showed dose-related maternal lethality, an acceptable nominal NOEL for maternal toxicity of 20 mg/kg/day was found, and (2) only the highest dose level, which was sufficient to kill most of the does, elicited identifiable developmental toxicity (early resorptions in surviving does). A study subsequently submitted (Argus study with DPR Record No. 115121) appears to cover a rational dosage range, is upgradeable, and does not indicate a "possible adverse effect". Thus there is no adverse effect indicated for the rabbit teratology study type. Aldous, 4/14/94.

062 115124. Summary of 2191. Contains significance of changes from acceptance criteria.

GENE MUTATION

Summary: The weight of evidence for gene mutation is negative. The one positive study in bacteria, Record Nos. 115126 and 115127, gave equivocal results in one strain of

Salmonella, TA100. Both studies using mammalian cells (#115125 and #128895) were negative. No consistent evidence for induction of gene mutations has been reviewed at this time (Gee, 4/21/94).

** 063 115125, "Blazer* Herbicide Technical CHO/HGPRT Gene Mutation Assay", (S. Foxall, G. Muller and J.P. Frank, Rohm and Haas Co., Reg. Document No. BASF: 87/5062, November, 1986). Blazer*, purity 42.8%, at concentrations of 325, 350, 375, 400, 425 or 450 µg/ml with metabolic activation and at 450, 500, 550, 600 or 650 µg/ml without metabolic activation (concentrations not corrected for purity), was tested to determine the potential to induce mutations at the HGPRT locus in Chinese hamster ovary cells. Exposure time was 5 and 18-20 hours with and without metabolic activation, respectively. There were no evidence of induced mutations with or without metabolic activation. ACCEPTABLE. (Kishiyama and Gee, 3/4/94)

** **064 115126**, **115127** "Blazer* Technical: Microbial Mutagenicity Assay", (C.A. Black and J.P. Frank, Rohm and Haas Co., Springhouse, PA, Reg. Doc. no. 87/5060, October, 1986). Blazer*, (technical sodium acifluorfen), purity 42.8%, at concentrations of 0 (saline buffer), 50, 200, 500, 2000 or 5000 µg/plate with and without metabolic activation (Aroclor-induced rat liver S-9) was evaluated for mutagenic activity in Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 after a 72 hour exposure period. Triplicate plates with a repeat assay with TA100. **The number of revertants increased (1.6 to 1.8 fold) for the initial and the repeat tests at test article dose level 5000 µg/plate with metabolic activation (S-9 mix) on Salmonella typhimurium strain TA100.** By the usual criteria of having at least a two-fold increase over the spontaneous rate, the response with TA100 is of questionable significance. No positive controls without activation. ACCEPTABLE. (Kishiyama and Gee, 4/13/94)

012 2189, Scribner, H.E., "RH-6201 (TD-77-287) Microbial Mutagen Assay - Salmonella typhimurium (Ames Test)", (Rohm and Haas Co., Org. Rpt. no. 78P-4, 11/15/77). RH-6201, 94%, at concentrations of 0, 1, 10, 50, 100, 500, 1000, 1500 or 2000 µg/plate with and without metabolic activation (S-9 mix) were evaluated for mutagenic activity in Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537. No increase in revertants. UNACCEPTABLE. (no justification of low level [2 mg/plate] selection as the high dose; no individual plate counts; no controls for S-9; no repeat experiment. (J. Remsen, 7/10/85).

001 2105, Brusick, D., "Mutagenicity Evaluation of RH 6201 Final Report - Reversion of Saccharomyces cerevisiae and Salmonella typhimurium", (Litton Bionetics Inc., LBI Proj. No.

2547, 1/17/76). RH6201, at concentrations of 0, 5, 50, 250 or 500 µg/plate with and without metabolic activation (S-9 mix) were evaluated for mutagenic activity in S. cerevisiae strain D4 and Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537. UNACCEPTABLE (insufficient information for evaluation; no dose selection rationale; number of plates/dose not given). (J. Remsen, 7/8/85).

363-067 128889 "An Ames Salmonella Microsome Mutagenesis Assay for Determination of Potential Mutagenicity of Acifluorfen" (C. A. Schreiner, study director, Mobil Environmental Health Sciences Laboratory, NJ, 5/27/80, Study No. 343-80) Acifluorfen, 99% pure, adjusted to pH 7.1 with NaOH, was tested with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 with and without rat liver activation. Concentrations were 0 (water), 47, 152, 488, 1562 or 5000 µg/plate. Number of plates per concentration were not given. Single trial. Data are reported as averages of colony counts. No evidence of increased reversion rate but cytotoxicity was reported at 5000 µg/plate in 4/5 strains. UNACCEPTABLE (number of plates per concentration not stated, no individual plate counts given). Upgradeability not certain. **No adverse effect indicated**. (Gee, 4/15/94)

363-067 128891 "An Ames Salmonella/Mammalian Microsome Mutagenesis Assay for Determination of Potential Mutagenicity of Tackle 2S MC10978" (C. A. Schreiner, Study Director, Mobil Environmental and Health Science Laboratory, 6/10/80) Tackle 2S, diluted from acifluorfen, was tested with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538 with and without activation with Aroclor 1254 induced male rat liver microsomes. Concentrations of Tackle 2S used were 0 (water), 0.09, 0.2, 0.4, 0.85 or 1.8 mg per plate. Number of plates not stated [protocol indicates a minimum of 2]. No increase in reversion rate was reported and the highest concentration was toxic. **No adverse effect indicated**. UNACCEPTABLE but possibly upgradeable with submission of the individual plate counts and justification for using Tackle 2S. (Gee, 4/15/94)

363-067 128894 "Mutagenicity Evaluation of MCTR-170-78 in the Ames Salmonella/Microsome Plate Test: Final Report" (D. R. Jagannath, Study Director, Litton Bionetics, January, 1979, LBI Report 20988) MCTR-170-78 (no further identification or purity) was tested with

Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538 and with Saccharomyces strain D4, with and without Aroclor 1254 induced rat liver activation. Concentrations were 0 (DMSO), 0.5, 1.0, 10, 100, 500, 1000 or 2000 (repeat assay) µg/plate. Number of plates per concentration is not stated but the single table of data implies a single plate per strain per concentration. Repeat assay with TA1535 with activation (positive control lost in first trial) and with TA1537 with and without activation. No evidence of an increase in reversion rate. **No adverse effect indicated**. UNACCEPTABLE, not upgradeable (single plate per concentration), test article not adequately identified). (Gee, 4/15/94)

363-067 128895 "A Murine Lymphoma (Heterozygous for Thymidine Kinase) Mutagenicity Assay for the Determination of Potential Mutagenicity of Tackle" (C. A. Schreiner, Study Director, Mobil Environmental Health Sciences Laboratory, Study No. 512-80, 11/12/80) Tackle 2AS herbicide (no purity or composition included) was tested with murine lymphoma cells, L5178Y, with and without Aroclor 1254 induced rat liver activation. Concentrations tested were 0 (PBS), 0.11, 0.19, 0.32, 0.56, 0.97 or 1.7 µl/ml cell suspension without activation and 0.8, 0.11, 0.19, 0.32 and 0.56 µl/ml with activation - described as µl Tackle 2AS/ml at an equivalent of active ingredient (sodium salt) of 227.8 µg/µl Tackle 2AS. Length of the exposure is not given. Mutation frequency presented in graphic form only. No induction of mutation was reported. **No adverse effect indicated**. UNACCEPTABLE (report lacks information on conduct of the study and the results for an independent evaluation). Upgrade unlikely. (Gee, 4/15/94)

CHROMOSOME EFFECTS

Summary: Two of the four studies reviewed may be upgradeable with submission of additional information as described in the review worksheets. Acifluorfen appears to have an effect on chromosomes (Gee, 4/21/94).

065 115128, 115130 "Blazer* Herbicide In Vivo Cytogenetic Study in Mice", (R.L. Yu, J.L. James and J.P. Frank, Rohm and Haas Co., Reg. Document No. BASF: 87/5063, November, 1986). Blazer*, purity 42.8%, dark brown liquid, at concentrations of 0 (distilled water), 100, 500, or 1000 mg/kg (42.8, 214 or 428 mg a.i./kg) was administered as a single dose by gavage to 5

Charles River mice/sex/treatment with sacrifices at 6, 27 and 51 hour post dosing. Blazer dose levels under the conditions of this study did not induce chromosomal aberrations in bone (femur) marrow cells. UNACCEPTABLE. Dose selection needs clarification in terms of the LD_{50} - whether doses were based on a.i. or 42.8% material) (Kishiyama and Gee, 4/13/94)

363-067 128896 "Drosophila Mutagenicity Assays of Mobil Chemical Company Compound MC 10109" (J. Bowman, Study Director, Utah State University Foundation, 4/13/81) Tackle 2S, MC 10109, lot LCM 266830-7, was tested for effects on the chromosomes of Drosophila. No purity of the test material. Five assays were evaluated: Induction of mosaics in female eyes, Y chromosome loss, induction of dominant lethal mutations, bithorax test of Lewis, and sex-linked lethals. Two were positive when males were treated with Tackle 2S at 15 mg/ml for 24 hours: loss of the Y chromosome and induction of dominant lethals. **Possible adverse effect indicated**. UNACCEPTABLE (missing information on conduct of the study, justification for treatment time and needed information on test material). (Gee, 4/15/94)

363-067 128897 "Metaphase Analysis of Rat Bone Marrow Cells Treated In vivo with Tackle 2S." (C. A. Schreiner, Study Director, Mobil Environmental and Health Science Laboratory, 3/13/81) Tackle 2S (no purity given) was given for 5 consecutive days to male Sprague-Dawley rats at 0 (Methocel K4M Premium), 0.37, 1.11 or 1.87 gm/kg by oral intubation. A total of 6 per dose were used. Cyclophosphamide was the positive control. Animals were sacrificed at 6(?) hours after the last dose. Fifty cells per animal were scored when possible. Summary data only that do not indicate a clastogenic effect. **No adverse effect indicated**. UNACCEPTABLE (report lacks details, test article not technical material, single sex only with no justification, no dose justification, no individual data, others). Not upgradeable. (Gee, 4/18/94)

363-067 128900 "Activity of T1689 in the Dominant Lethal Assay in Rodents." (D. L. Putman, Study Director, Microbiological Associates, 9/23/81) Tackle 2S, 236 mg/ml solution of active ingredient (no further identification) was given to 10 male Sprague-Dawley rats at doses of 0 (water), 80, 360 or 800 mg/kg (not stated if based on Tackle or active ingredient) for 5 consecutive days by oral gavage. Males were mated with two females per male for 5 days per week for 7 weeks. Females were sacrificed 14-15 days after the mid-point of the mating

period. Fertility index, implantations per pregnant female, corpora lutea, preimplantation loss, dead implants and live implants were scored. Although there is no dose response, the preimplantation loss was increased statistically over the concurrent controls. **Possible adverse effect indicated.** UNACCEPTABLE (no individual data, inadequate number of pregnant females for analysis, no justification for stopping matings at 7 weeks or for the dosing regimen, no dose justification, use of other than the technical grade and the basis for the doses unclear, others.) Not upgradeable. (Gee, 4/19/94)

DNA DAMAGE

Summary: Three of the four studies had induction of unscheduled DNA synthesis as the endpoint. All were negative. The study using Saccharomyces and measuring cross over events was positive in two trials. This finding is consistent with the results in Drosophila and the dominant lethal assay in rats. A possible adverse effect is noted (Gee, 4/21/94).

** 066 128432 "BLAZER Herbicide Technical In vitro Unscheduled DNA Synthesis Assay" (Muller, G., Rohm and Haas, Document No. BASF 87/5061, November, 1986.) Blazer (acifluorfen, sodium salt), 42.8% active ingredient, was assayed for induction of unscheduled DNA synthesis with primary hepatocytes from a male rat. Concentrations ranged from 1.0 to 1000 µg/ml, corrected for active ingredient. A total of thirteen concentrations were used but only 6 were scored: 1.0, 1.8, 3.2, 5.8, 10 and 17.8 µg/ml after 19 hours of treatment. Viability was 77% or greater (by dye exclusion) at these concentrations. 2-Acetylaminofluorene was the positive control and functioned as expected. Fifty cells per each of the three slides per concentration were scored for net nuclear grain count. There was no evidence of unscheduled DNA synthesis with acifluorfen treatment. The individual cell data are not included but the means for each of the three slides per concentration are included. ACCEPTABLE with the above deficiency noted. (Gee, 4/12/94)

363-067 128898 "An Investigation of the Potential of Tackle and Aqueous and Hexane Extracts of Tackle to Induce Unscheduled DNA Synthesis in the in vivo-in vitro Hepatocyte DNA Repair Assay in Rats and Mice." (Mirsalis, J. C., SRI International, 5/23/83) Tackle and

aqueous and hexane extracts of Tackle were tested with male F-344 rats (Tackle only) or male B6C3F1 mice. Doses were given 2 or 12 hours before sacrifice and the isolation of primary hepatocytes. Tackle: 0 (water), 10, 40 or 200 mg/kg; aqueous extract of Tackle: 0 (water), 20, 150 or 700 mg/kg; hexane extract of Tackle: 0 (water), 50, 200, 700 or 1000 mg/kg. Dimethylnitrosamine was the positive control. Net nuclear grains were scored from 3 animals per group per dose. No evidence of induction of unscheduled DNA synthesis or increase in cells in repair were reported. **No adverse effect indicated**. UNACCEPTABLE (numerous deficiencies including use of males only, no dose justification, no justification for sacrifice times, use of other than the technical grade material) (Gee, 4/18/94)

363-067 128899 "Mutagenicity Evaluation of 06238001 Lot LCM 266830-7 in the Mitotic Recombination Assay with the Yeast Strain D5." (D. R. Jagannath, Study Director, Litton Bionetics, January, 1981) Mobil compound #06238001, lot LCM-266830-7, was tested with Saccharomyces cerevisiae strain D5 as a 29.7% solution in NaOH adjusted to pH 8.0. Two trials were conducted for cross over events with and without activation with rat liver microsomes. Concentrations in trial 1 were 0 (water), 0.1, 1.0, 5, 10 or 50 µl/sample for 3 hours followed by plating. In the second trial, 0, 2.5, 5.0 or 7.5 µl without activation and 0, 7.5, 10 or 25 µl/sample with activation. Increases in recombination events occurred in both the presence and absence of activation. **Possible adverse effect indicated.** UNACCEPTABLE (test material needs to be defined, the number of replicates needs to be submitted, individual data are needed and a QA statement should be submitted.) Possibly upgradeable. (Gee, 4/18/94)

363-067 128901 "Evaluation of 06238001 in the Primary Rat Hepatocyte Unscheduled DNA Synthesis Assay." (B. C. Myhr, Study Director, Litton Bionetics, 4/29/81) Compound 06238001, lot LCM 266830-7 (identified as Tackle 2S on cover page) was tested with primary rat hepatocytes for the induction of unscheduled DNA synthesis. Cultures in triplicate were incubated for 18 hours with concentrations of 0 (WME medium), 0.1, 0.25, 0.5, 1.0, 2.5, 5, 10, 25 or 50 µg/ml final concentration. At 50 µg/ml, survival was 2.1% of control. No evidence for induction of UDS was reported. **No adverse effect indicated.** UNACCEPTABLE (test material needs description and justification if other than the technical grade, data on cytoplasmic and nuclear grain counts are needed). Upgrade may be possible. (Gee, 4/19/94)

NEUROTOXICITY

Not required at this time.